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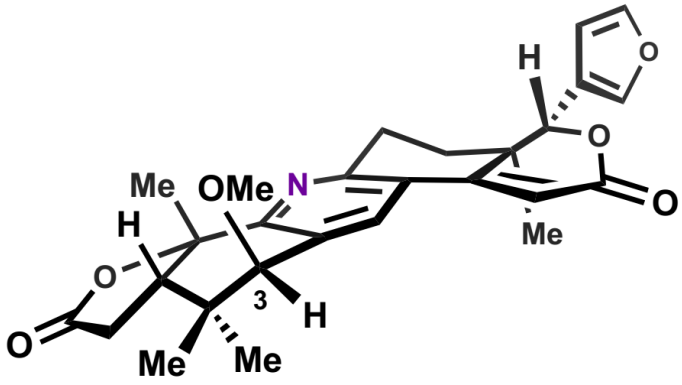
Communication

Total Synthesis of (+)-Granatumine A and Related Bislactone Limonoid Alkaloids via a Pyran to Pyridine Interconversion

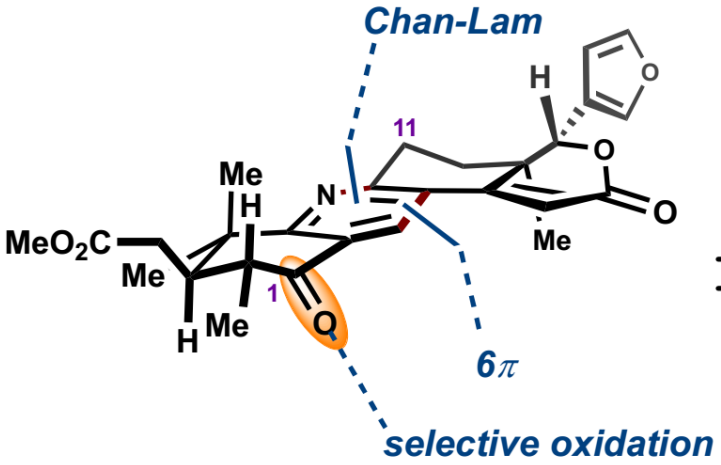
Alexander W. Schuppe, Yizhou Zhao, Yannan Liu, and Timothy R. Newhouse



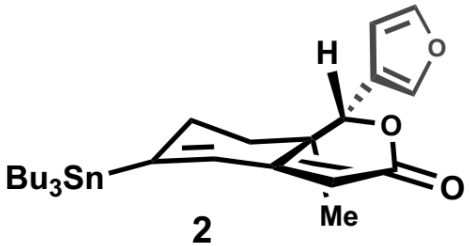
(+)-granatumine A (6)
[PTP1B inhibitor]

- bislactone limonoid alkaloid
- isolated from the Chinese mangrove (*Xylocarpus granatum*)
- Inhibitory activity against PTP1B

A. Prior Work:



xylogranatopyridine B (1)
[no known activity]



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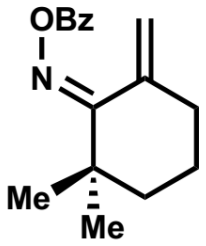

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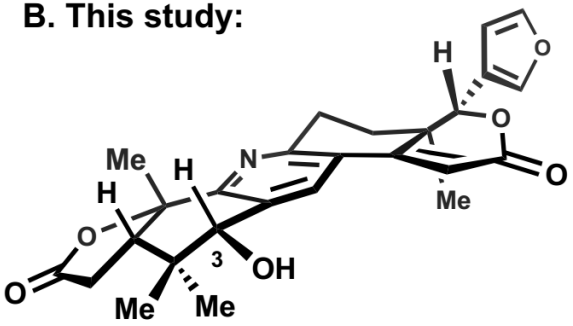
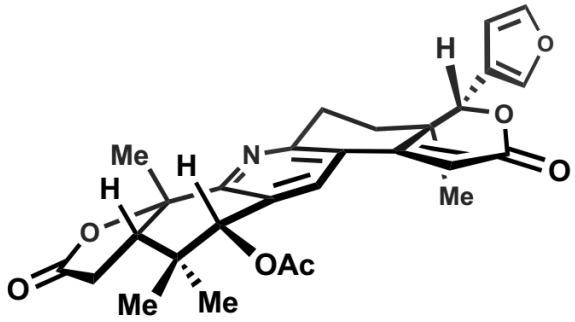
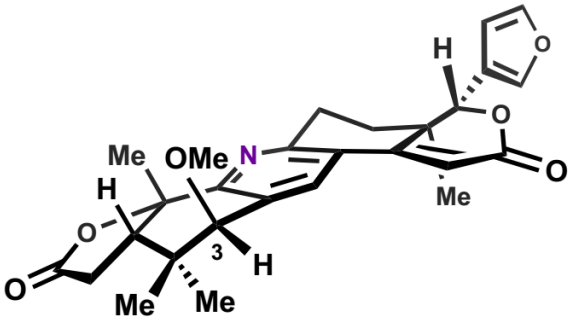
B. This study:



(+)-xylogranatin F (4)
[proposed structure]



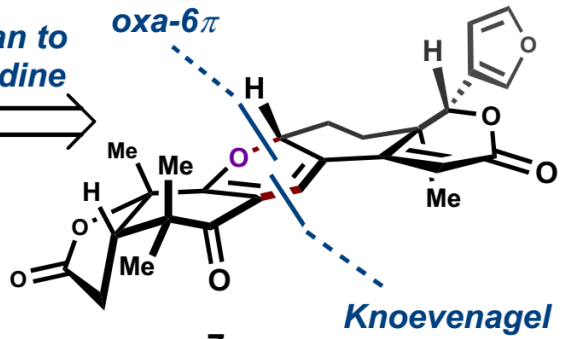
(+)-xylogranatin G (5)
[proposed structure]



(+)-granatumine A (6)
[PTP1B inhibitor]

pyran to pyridine

selective oxa-6π



Knoevenagel

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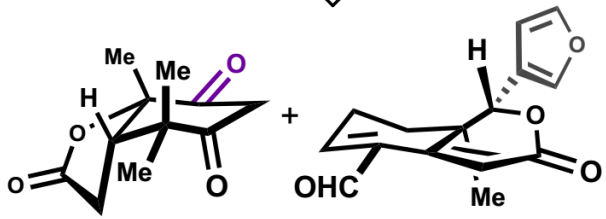
New synthetic challenges:

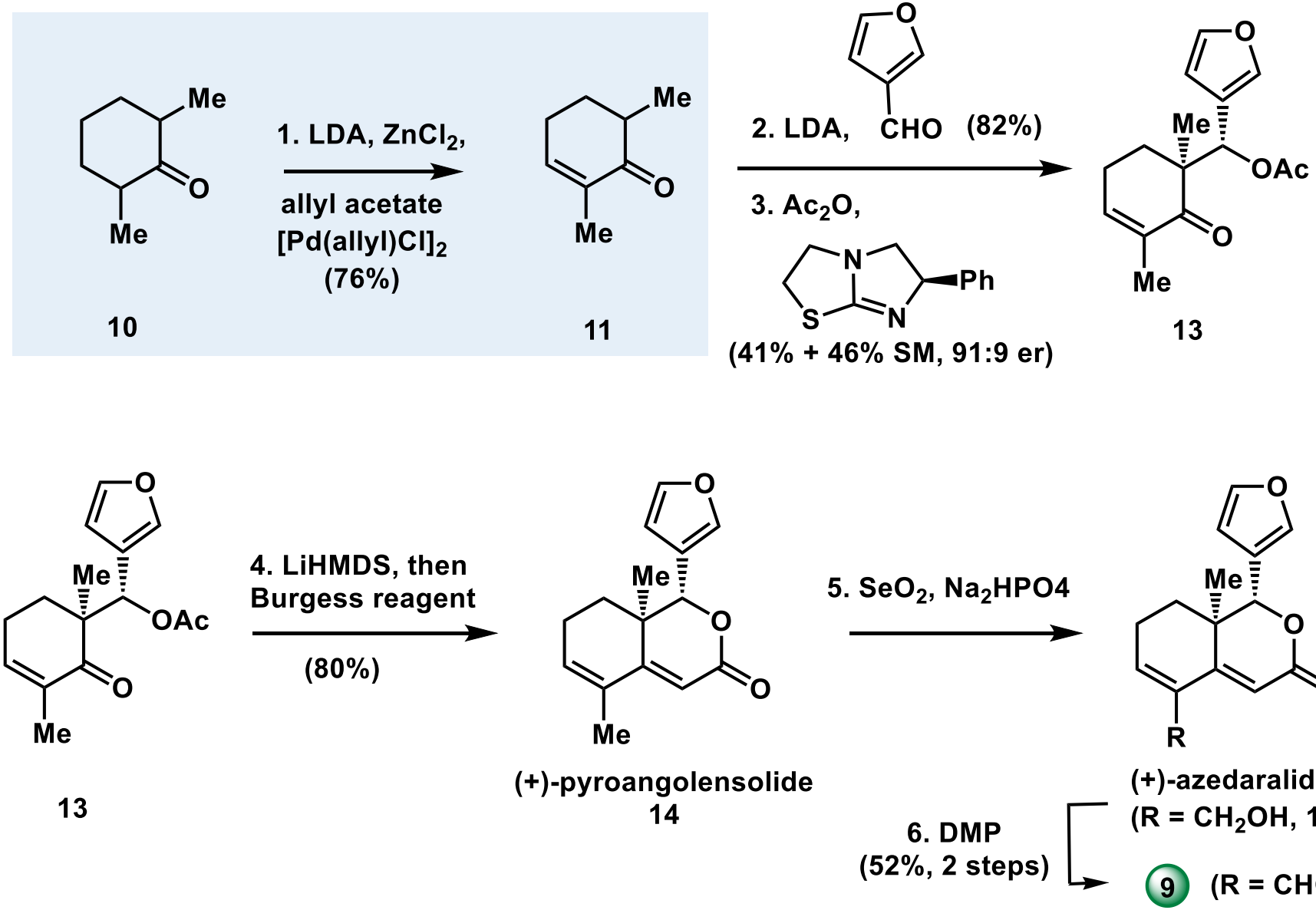
- reorganized A-ring with a fused lactone
- stereogenic oxygen substituents

Key methodological advances:

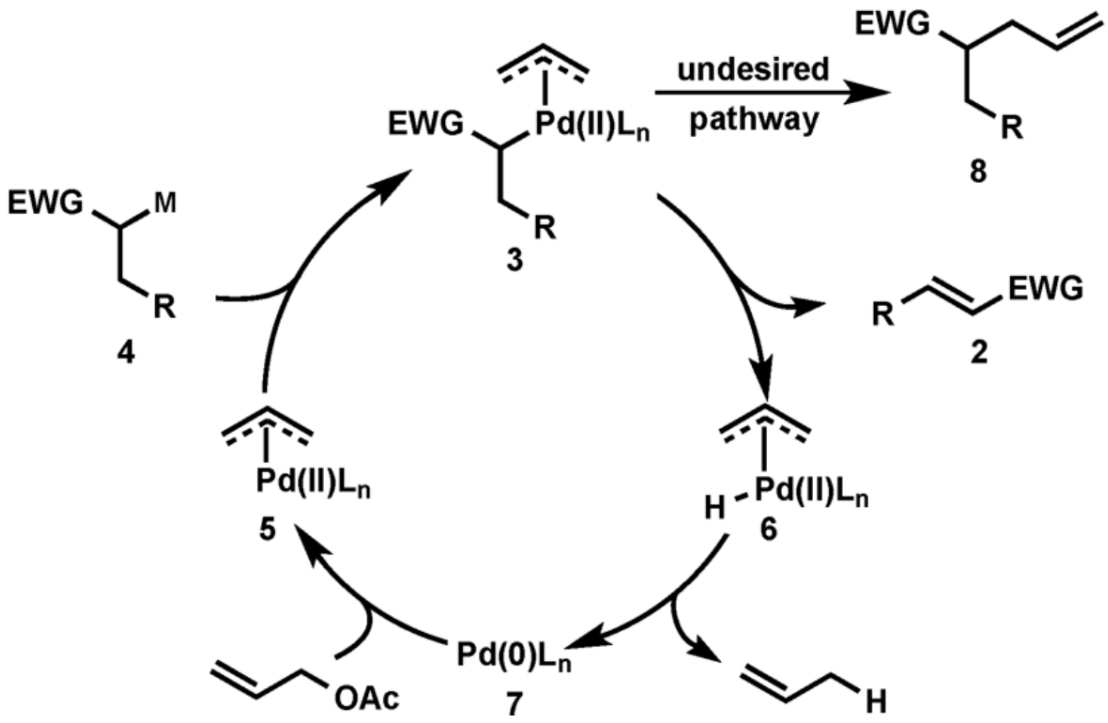
- Pd-catalyzed epoxide opening
- pyran-pyridine transformation



8 **9**


Me
O
Me
10
1. LDA, $ZnCl_2$,
allyl acetate
$[Pd(allyl)Cl]_2$
(76%)
Me
O
Me
11
O
CHO
2. LDA,
(82%)
3. Ac_2O,
N
Ph
S
N
(41% + 46% SM, 91:9 er)
O
Me
OAc
O
Me
13
O
Me
OAc
O
Me
13
4. LiHMDS, then
Burgess reagent
(80%)
O
Me
O
O
Me
(+)-pyroangolensolide
14
5. SeO_2, Na_2HPO4
O
Me
O
O
R
(+)-azedaralide
(R = CH_2OH, 15)
6. DMP
(52%, 2 steps)
9
(R = CHO)

Dehydrogenation strategy:



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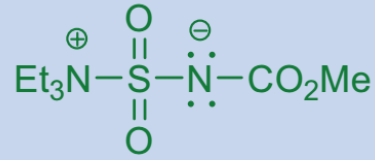
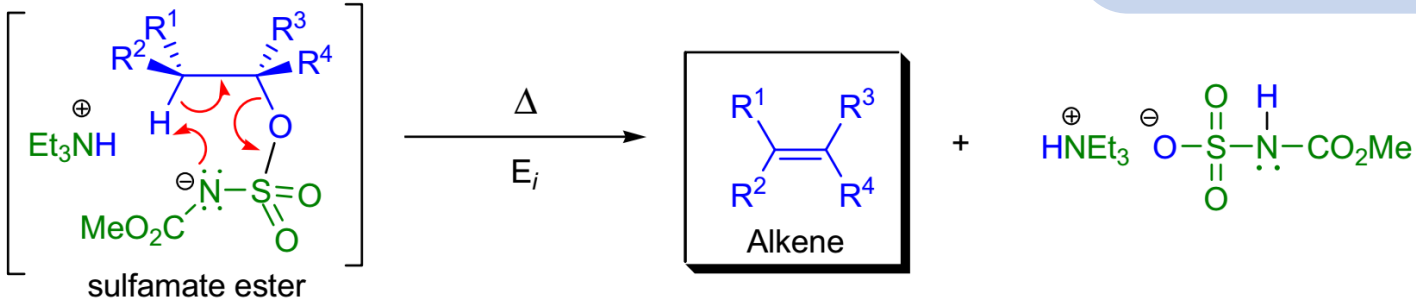
BURGESS DEHYDRATION REACTION



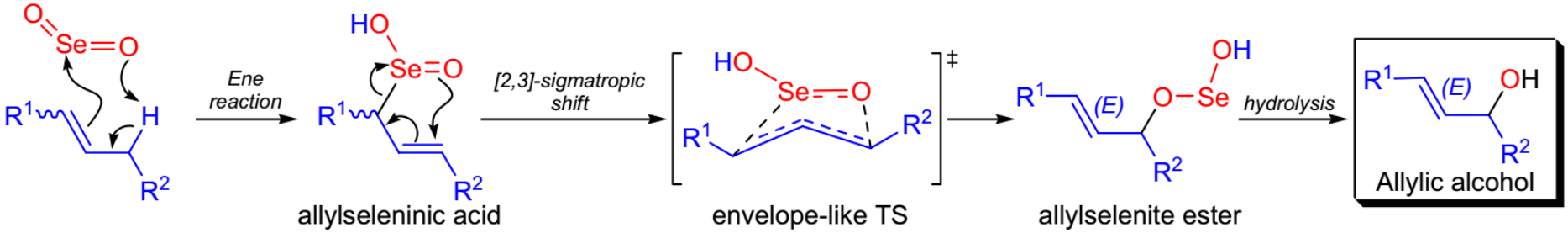
Burgess reagent



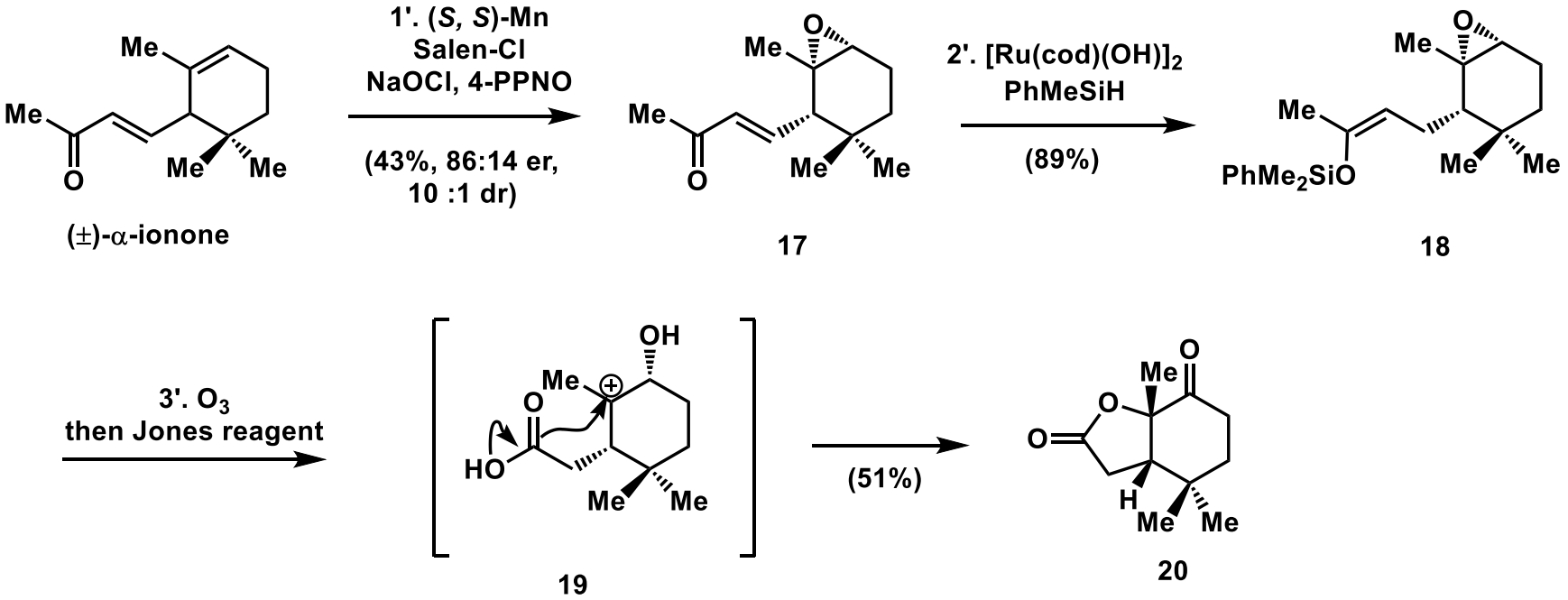
sulfamate ester

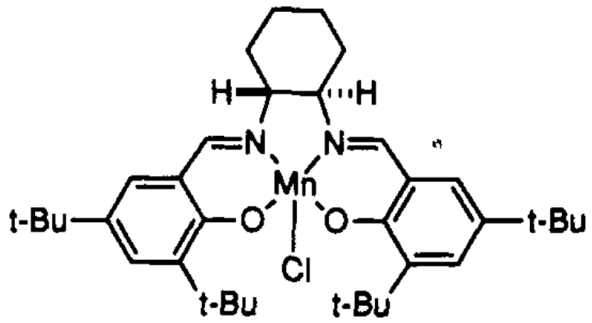
RILEY SELENIUM DIOXIDE OXIDATION

Oxidation of alkenes:

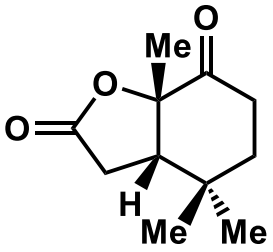


allylseleninic acid envelope-like TS allylselenite ester





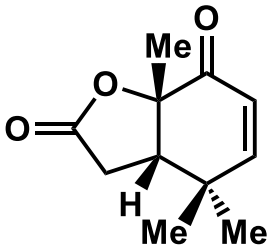
(*S, S*)-Mn Salen-Cl



20

4'. $Pd(TFA)_2$
DMSO, O_2

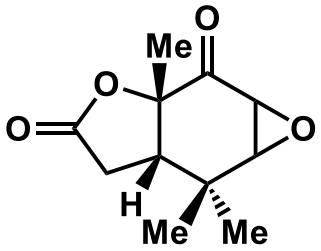
(92%)



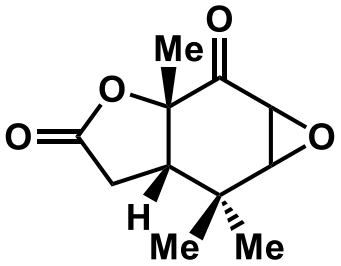
21

5'. urea·H_2O_2
DBN, H_2O

(67%, 1:1 dr)



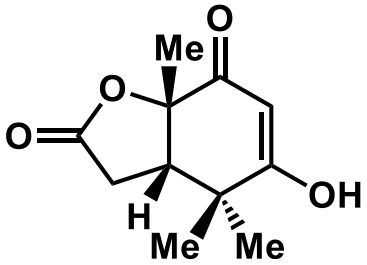
22



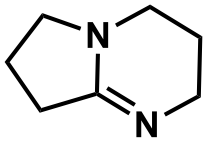
22

6'. $Pd(OAc)_2$, XPhos

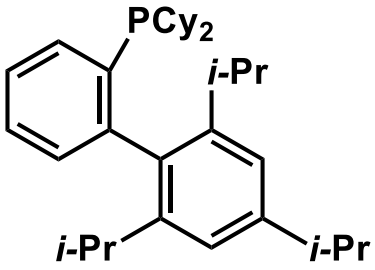
(90%)



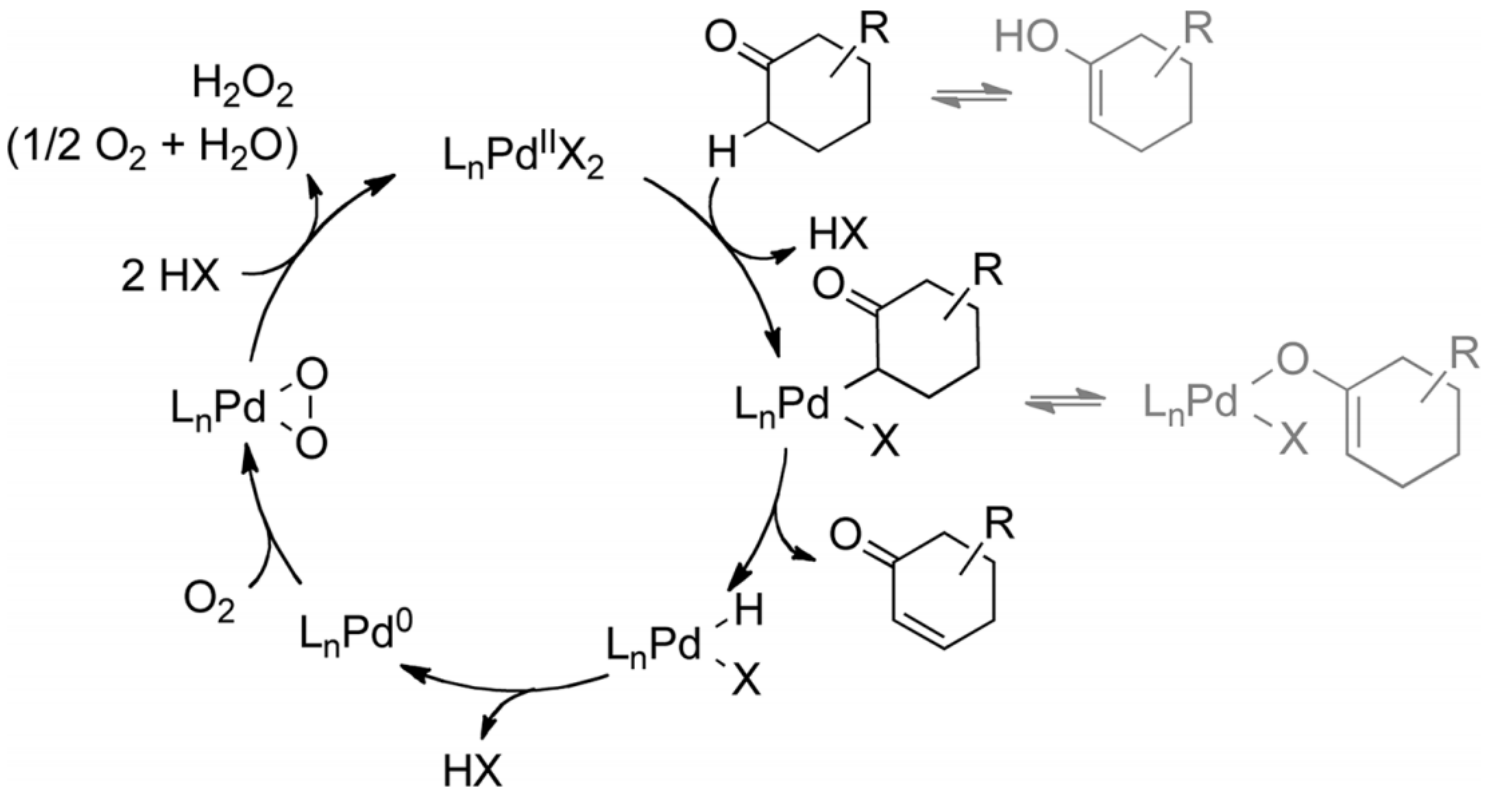
8



DBN



XPhos



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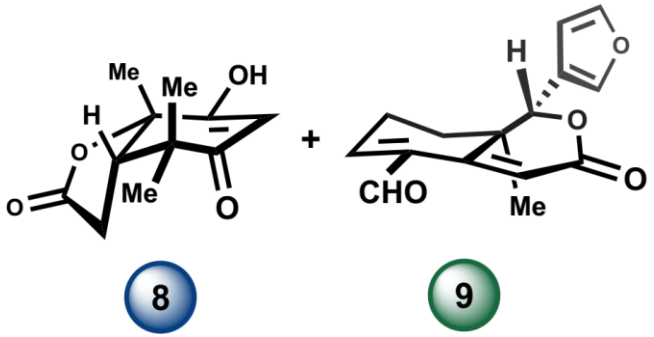
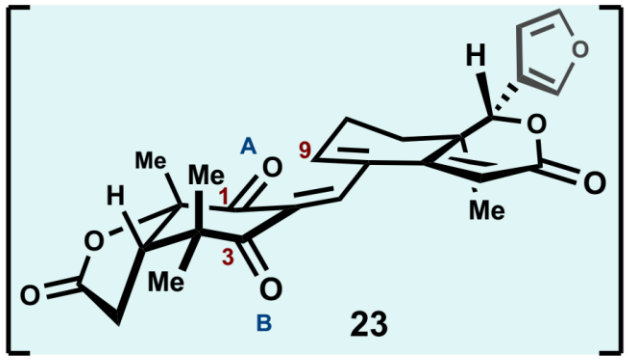
A.

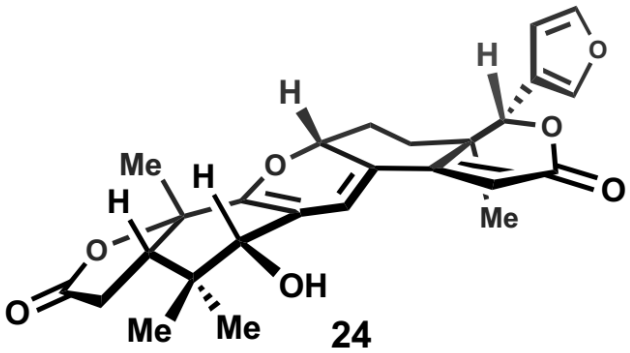


7. H_2N NH_2 • 2 AcOH



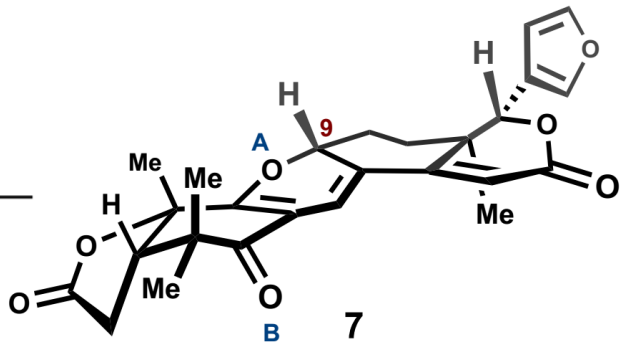
selective oxa-6π

(47%, >20:1 dr
>20:1 rr)

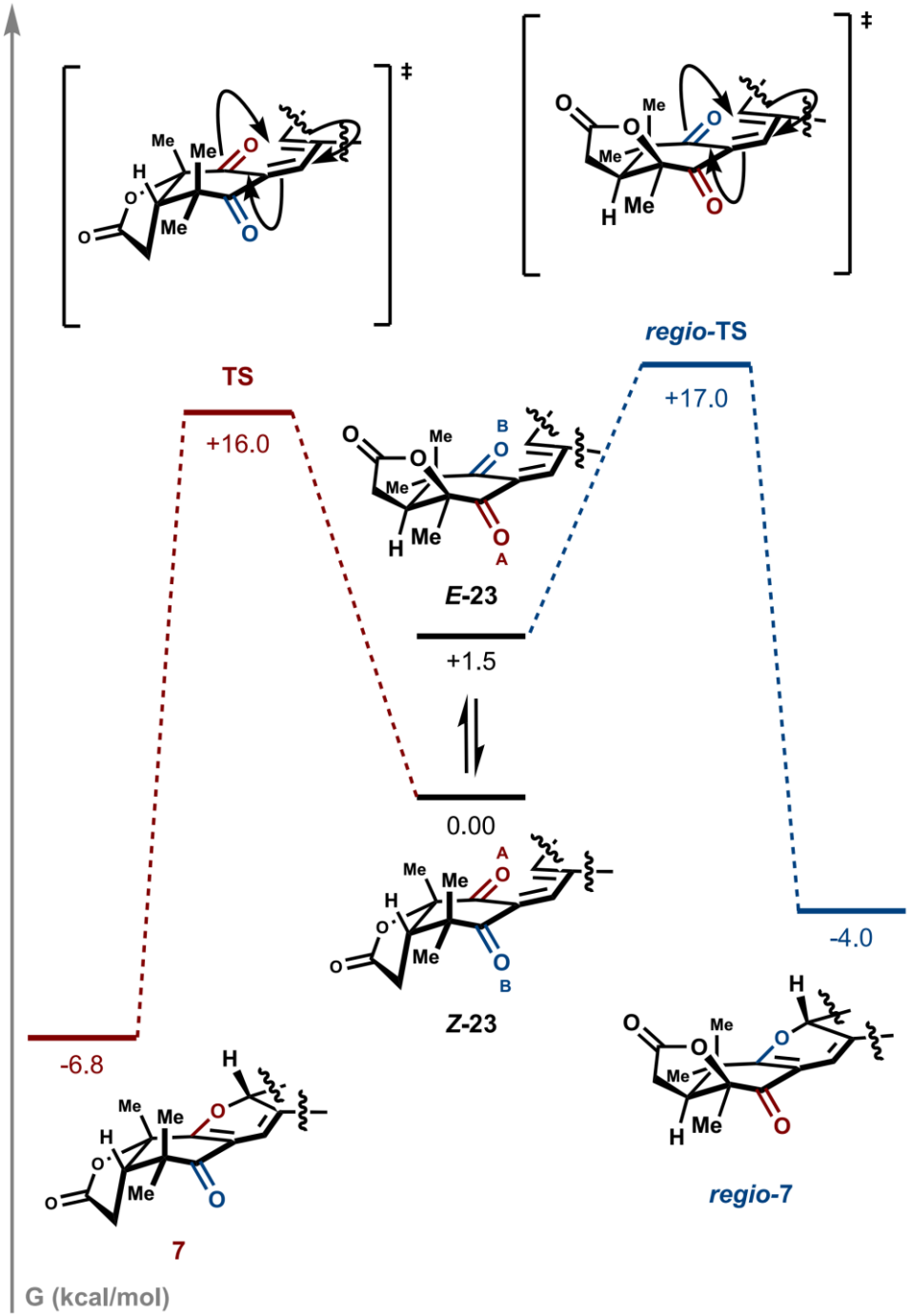


8. $LiBH_4$
$CeCl_3$, TFE

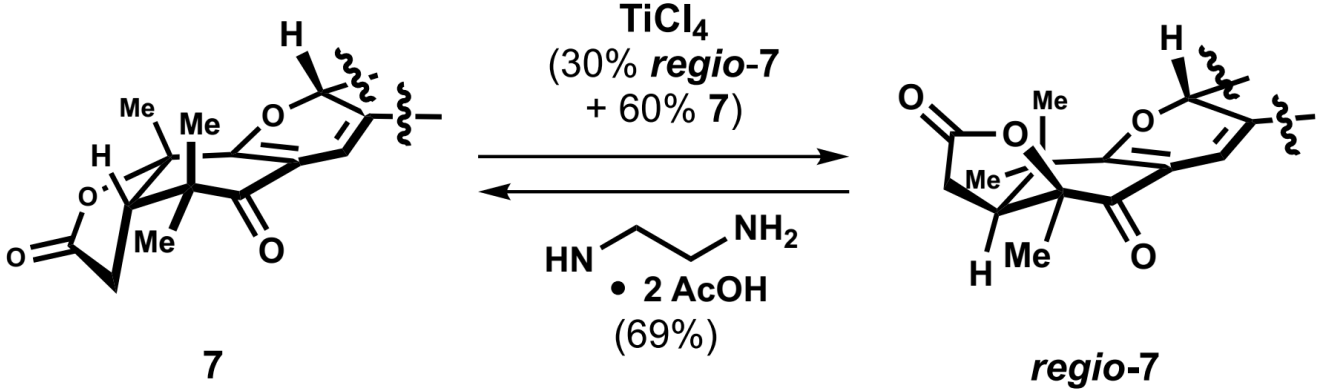
(61%
>20:1 dr)

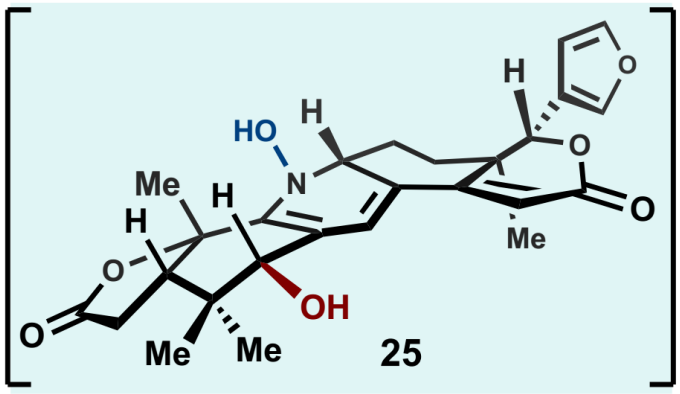


A. Computational investigations:



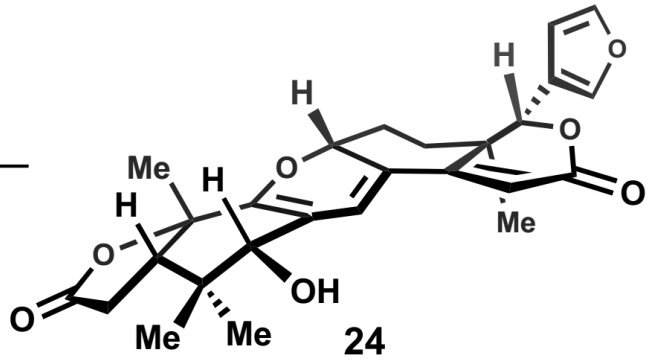
B. Interconversion investigations:



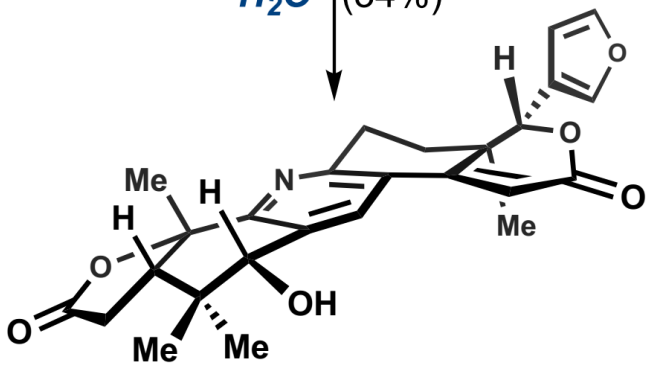


9. $HO\text{-}NH_2 \cdot HCl$
$LiOAc \cdot 2H_2O$

retro-oxa-6π, condensation, aza-6π



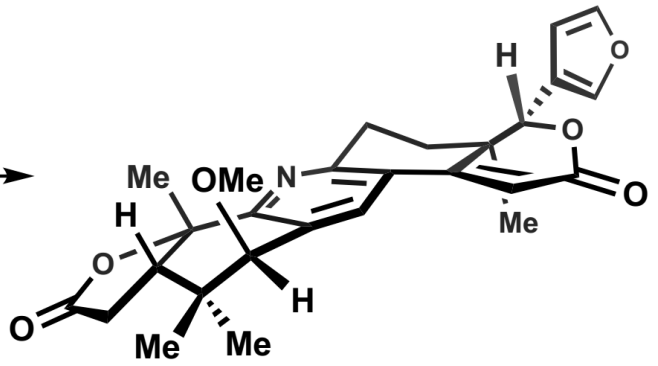
-H_2O (34%)



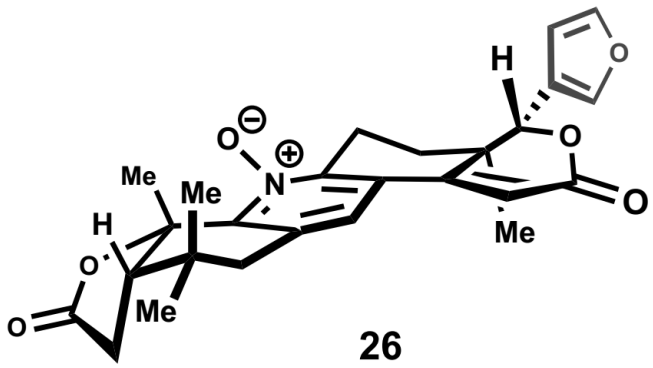
(+)-xylogranatin F (4)
[proposed structure]

10a. $SOCl_2$
then NaOMe

(82%, 1:1 dr)



(+)-granatumine A (6)



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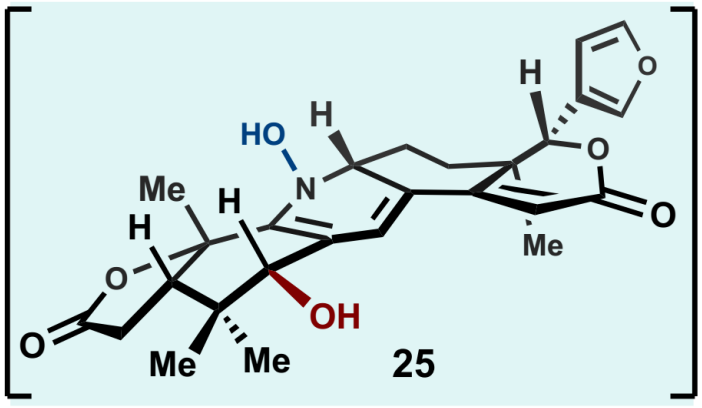
-H_2O

(35%)



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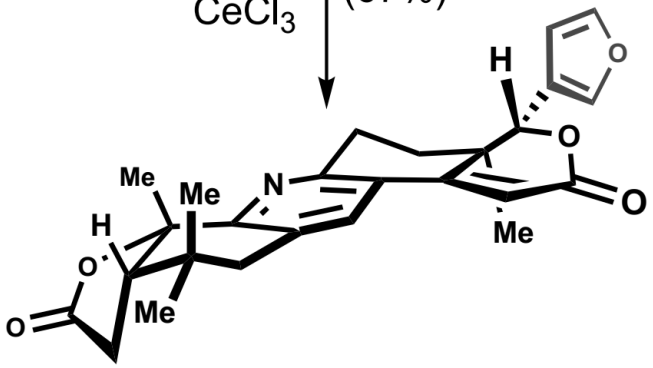
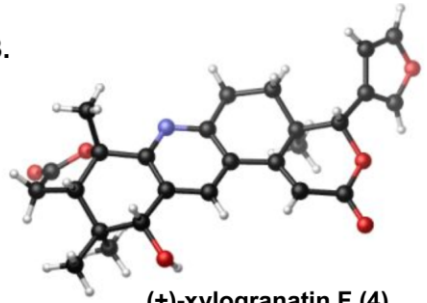
10b. Zn, $CeCl_3$

(67%)



(+)-3-deoxy-xylogranatin F (27)

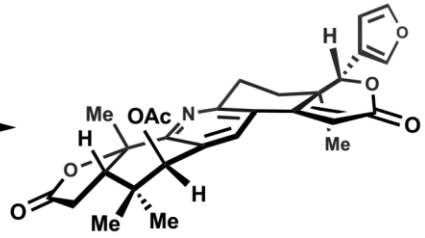
B.



(+)-xylogranatin F (4)
[X-ray of proposed structure]

10c. $SOCl_2$
then $Zn(OAc)_2$

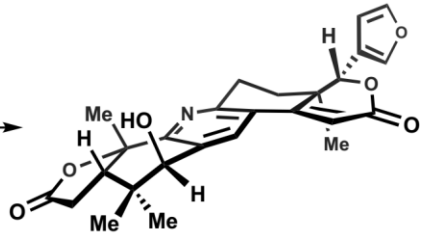
(74%, 1:1 dr)



(+)-xylogranatin G (28)
[revised structure]

11. K_2CO_3

(87%)



(+)-xylogranatin F (29)
[revised structure]